Therapeutic enquiries about biological agents as a tool to identify safety aspects and patterns of use

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ABSTRACT

Background Biotechnological agents (BA) are increasingly being used in clinical practice. We aimed to determine, whether enquiries about them to a therapeutic consultation service have also become more frequent, and to describe the information requested in these consultations.

Methods We retrospectively reviewed 14 104 therapeutic consultations collected in a computerised database between 2000 and 2014. Enquiries about BA (monoclonal antibodies, fusion proteins or cytokine antagonists) were chosen. Information on the type of BA, underlying condition, type of enquiry and affiliation of the enquirer was retrieved and compared with data from consultations about other agents.

Results During the study period, 365 enquiries about 30 different BA were received. Only 4% of them were received before 2004, while 48.8% were received after 2010. Rituximab, infliximab, adalimumab and etanercept were most frequently enquired about. Agent selection (n=184) and/or adverse effects (n=174) were the most frequent reasons for making an enquiry. Most enquiries about an agent selection were made about an off-label use (n=164), mainly for systemic autoimmune diseases (n=61). Over half of the enquiries about adverse effects were about their teratogenic potential (n=96). Enquiries about BA more often requested an opinion (87.7% vs 77.7%) were made by physicians (89.9% vs 76.9%), from a hospital (81.6% vs 44.5%) and regarded a specific patient (87.4% vs 74.5%).

Conclusions Therapeutic consultations about BA are increasing. Most of them are related to uncertainties of health professionals regarding any new medicine: their off-label use, actual adverse effects or the teratogenic potential of the involved agents.

and safety comes from the manufacturer and from clinical trials that have included not much more than hundreds of patients in selected pathologies. There are lots of doubts about these agents' efficacy or toxicity that only clinical practice can eventually clarify. Yet another problem is that, nowadays, the tremendous amount of new medical information is difficult to manage for clinicians as they can provoke information overload.⁵

Biotechnological molecules represent a valid example about newly approved therapeutic agents. Between 2008 and 2013, 30 new biotechnological agents (BA) gained Food and Drug Administration (FDA) approval.⁶ Since the European Medicines Agency (EMA) approved the first BA (follitropin-alfa) under centralised marketing authorisation, the number of marketed BA has increased. Currently, BA represent approximately 20% of all approved medications under centralised marketing in the European Union,⁷ and they contribute to an increasing pharmaceutical offer and expenditure.⁸ Adalimumab, etanercept, rituximab, infliximab, bevacizumab and trastuzumab, for example, are in the top 15 all-time selling drugs. Moreover, the inrush of BA has noticeably changed clinical practice in areas such as oncology⁹ and autoimmune diseases.¹⁰ Although, the approval process of any drug is based on clinical trials demonstrating their efficacy in specific indications for which they have been developed, BA are often used in clinical conditions different from those for which they were approved. In this context, many doubts about their efficacy and safety arise, and physicians often lack the information needed to resolve them.

Therapeutic consultations are a useful tool to obtain, select and evaluate the best information to resolve doubts about patient management in daily practice, and to detect clinical problems which have not been fully investigated.¹¹ Drug information services are an increasingly important component of the effort to promote the healthy, evidence-based use of medicines.¹² The nature of enquiries made to these services may provide understanding of the dilemmas brought about by prescribing in clinical practice, and can contribute in some way to the generation of new knowledge in clinical pharmacology.^{13–15} No studies have assessed the therapeutic consultations about BA and the type of information requested regarding those drugs. This study aimed to explore this issue by analysing the information on the characteristics of the consultations about BA.

METHODS

We carried out a retrospective longitudinal study from a computer database with 14 104 therapeutic consultations collected at the *Fundació Institut*

INTRODUCTION

Physicians raise an average of two questions for every three patients they see in office practice.¹ In some cases, this question refers to a particular patient affected by a condition that lies within a highly specialised area and requires factual information. At other times, physicians also need support, guidance and feedback confirmation from a colleague. Unfortunately, many times, these questions may remain unanswered, as this would require a time and expertise, that is, not always available.^{2–3}

Prescribing requires a diagnosis of a condition affecting a given patient, and to apply background knowledge about essential information on therapeutics.⁴ This is particularly difficult with recently approved products. When a drug is introduced into practice, almost all the information about efficacy

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Català de Farmacologia and clinical pharmacology service in *Vall d'Hebron University Hospital* in Barcelona. This therapeutic consultation service is free and independent being carried out by staff clinical pharmacologists, who are responsible for responding to enquiries. In addition, residents in training are also involved, who make a rotation of 6 months for this area during their postgraduate training. The response, usually in a document elaborated by clinical pharmacologists, contains the answer, a conclusion with a specific recommendation, and the bibliographic references used. After sending the document to the enquirer, it is included in a database in order to be used for a similar situation.

The therapeutic consultations received are systematically coded according to different variables.

This analysis was carried out during the period between January 1999 and December 2014. For this study, therapeutic consultations about certain recently marketed BA with immune modulating properties (monoclonal antibodies, fusion proteins and cytokine antagonists) were selected (the complete list is provided as online supplementary table S1). The study's reference group comprised all the consultations in which at least one of the agents enquired about belonged to this list. All other consultations comprised the control group. The features of the consultations in each group were compared.

The study variables included data of the therapeutic consultation, profession and institution of the consultants, drugs and diseases on which information was asked for, kind of requested information (an opinion regarding the therapeutic attitude or factual information), and the topic of the query. The topic was selected from a predefined dropdown list which includes: 'adverse effect', 'efficacy', 'interaction', 'intoxication', 'market', 'methodology', 'pharmacodynamics', 'pharmacogenetics', 'pharmacokinetics', 'pharmacy', 'selection' and 'general'. The term general is selected when the requested information is broader than what can be included under any combination of a couple of the other topics, and selection is used when information about the best therapeutic option in a given patient or situation, or about the appropriateness for using or not a specific drug (in practice, this label offers mostly a balanced account of the agent's efficacy and adverse effects). More than one topic can be chosen to define a single consultation. On the other hand, as far as the circumstance that prompted the consultation to be made, information on whether it referred to a specific patient or to a special population (eg, children, elderly individuals, pregnancy, breastfeeding, liver or kidney failure) was recorded.

The specific agent(s) involved are referred to both by their international non-proprietary name and anatomical therapeutic chemical (ATC) code. Diseases referring to the underlying condition in consultations about selection or efficacy of a drug were grouped into the ICD-10 chapters, and those referring to the nature of the adverse reaction in consultations about an adverse effect into the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes.

Since all variables were categorical, their absolute and relative frequencies were used for the analyses; intergroup comparisons, when appropriate, were performed with the χ^2 test. Statistical analysis was performed using the SPSS V.19.0 software package. A two-tailed $p=0.05$ was set as the limit for statistical significance.

RESULTS

A total of 14 104 enquiries were received during the study period; 365 of them (2.53%) were about at least one of the interest drugs. As shown in [figure 1](#), most of these consultations

were received in the latest years of the study. Noteworthy, only 15 of the total consultations regarding a BA were received before January 2003, while 178 of them were received after December 2011 (ie, 4.1% were received in the first 3 years, and 48.8% were received in the last 3 years of the study period). In contrast, the proportion of enquiries about non-BA received each year remained fairly constant, from a minimum of 758 (5.5% of those received over the whole study period) in 2000 to a maximum of 1047 (7.6% of the total in 2008) during the whole study period.

As compared with enquiries about other agents, those about BA were more likely to request an opinion (87.7% vs 77.7%), to have been made by a physician (89.9% vs 76.9%), working in a hospital (81.6% vs 44.5%) and to have been prompted by their actual or potential use in a specific patient (87.4% vs 74.5%). All differences were statistically significant ($p<0.001$).

The main reasons to raise a query about a BA were concerns about their adverse effects ($n=174$ about 186 agents), and/or the request for guidance in agent selection ($n=184$ about 198 agents). [Table 1](#) shows the distribution of consultations about these aspects that were made regarding BA and non-BA. Overall, consultations about BA were more likely to have been made regarding drug selection, while consultations about other agents were more likely to have been made about adverse reactions; all differences were statistically significant ($p<0.001$). As for the rest of enquiries received about BA, 18 were made about an interaction, 9 about pharmacokinetics, 7 about market, 2 about pharmacodynamics and pharmacy, and 1 about methodology and pharmacogenetics. There were 30 enquiries placed under the heading general. These numbers were felt to be too small to allow for further analysis.

Consultations about BA were made regarding 30 different compounds (see [table 2](#)). The most frequently drugs enquired about were rituximab, infliximab, adalimumab and etanercept. Queries for anakinra, omalizumab and rituximab were preferentially made regarding their selection, while queries about adalimumab, etanercept and infliximab were preferentially made regarding their adverse effects. A selection of illustrative examples of the therapeutic consultations about BA that were received, both regarding drug selection and adverse effects is presented in the [box 1](#).

Questions about selection were made mainly regarding the paradigmatic diseases with immune mediated pathophysiology in each specialty area. Out of the 184 enquiries, 61 (33.2%) were made about a musculoskeletal, 23 (12.5%) about a dermatological, 19 (10.3%) about a digestive, 13 (7.1%) about a neurological and 11 (6.0%) about a respiratory disease. In 160 of these enquiries (87.0%), an opinion about the appropriateness of a specific agent for a particular patient was requested. At the time they were made, the vast majority of enquiries regarding the six agents most frequently enquired about (82.5%) were about an off-label use ([table 3](#)).

The teratogenic potential was the most frequent question about adverse effects (96 out of 174 therapeutic consultations (55.2%). More than half (56; 58.9%) were about a woman that had become pregnant while she or her partner were taking the medication, and 39 (41.1%) about the teratogenic potential of an agent taken by a member of a couple planning a pregnancy. Only 16 of the exposures that had prompted these consultations (16.8%) were paternal. The MedDRA organ system classes for which more than five consultations were received were blood diseases ($n=12$: thrombocytopenia (5), anaemia (4) and neutropenia (3)), respiratory diseases ($n=8$: interstitial lung disease (5), asthma (1), cough (1) and not otherwise specified lung disease

Figure 1 Number of consultations received each year by agent group.

(1)) and vascular diseases ($n=7$: thrombosis (5) and pulmonary embolism (PE) (2)). Fifteen of the consultations that had been made about an adverse effect actually experienced by a particular patient were forwarded to the regional pharmacovigilance service. These suspected adverse drug reactions included two cases of pancreatitis, a PE and a case of polyneuropathy in patients taking etanercept, two cases of interstitial pneumonitis and a case of atrial fibrillation in patients taking rituximab, a case each of interstitial pneumonitis, pleuropericarditis and neutropenia in patients taking infliximab, a stroke in a patient taking adalimumab, a skin reaction in a patient taking ranibizumab, a case of fever in a patient taking omalizumab, a case of PE in a patient taking denosumab and a case of tuberculosis in a patient taking anakinra.

DISCUSSION

Our study shows that therapeutic consultations about BA are progressively increasing, and most of them are related to three important uncertainties of health professionals regarding any new medicine: their off-label use in systemic autoimmune diseases, actual adverse effects or the teratogenic potential of the involved agents. To our knowledge, this is the first study to analyse enquiries about BA to a therapeutic consultation service. Unsurprisingly, the main doubts about their use are those about the use of any newly marketed agent.

The task of trained professionals, either clinical pharmacologists or pharmacists as experts in therapeutic consultation services and drug information services, is valuable. They provide factual information that serves as evidence base for better prescription and an insight into the areas of uncertainty most commonly encountered by prescribers and warn of possible previously unrecognised adverse drug reactions. With this aim,

we used our database to describe the temporal trend and specific features of therapeutic consultations about BA received at our institution during the last 15 years. Noteworthy, drug information services, including therapeutic consultations, have a direct impact on patient care. Responses are translated in clinical actions to ensure safe drug therapy. Coordination of both clinical pharmacologists and pharmacists to offer drug information to physicians ensure a more complete and efficient service to promote optimal drug use.¹⁶

Although, some results could have been reasonably foreseen, others merit special consideration because they reflect health professionals' information needs about new medicines. In this scenario, clinical pharmacology may have a potential role to enhance the information provided by the manufacturers. An opinion for a specific patient was more frequently asked for in consultations about BA than for the rest of enquiries. This can reflect the need for another professional's opinion to support a decision regarding the prescription of new and expensive drugs.^{17,18} When treatment with a new biological agent is being considered for a specific patient, health professionals request information about the different aspects not clearly elucidated in the early postmarketing time: strength of evidences to recommend and off-label use, information about potential teratogenic effects and suspicion of adverse effects.

Table 1 Comparison of the main reasons for received consultations regarding biotechnological and other agents

	Biotechnologicals (N (%))*	Other agents (N (%))*
Selection	159 (43.6)	2348 (17.1)
Efficacy	25 (6.8)	185 (1.3)
Adverse reaction	174 (47.7)	9296 (67.7)
Other†	56 (15.3)	3534 (25.7)
Total	365 (100)	13 739 (100)

*The sum is larger than the total because consults in which more than one aspect of drug use was simultaneously enquired about was included under all applicable headings.

†Includes interaction, intoxication, market, methodology, pharmacodynamics, pharmacogenomics, pharmacokinetics, pharmacy and general.

Table 2 Summary of the drugs involved in consultations about biotechnological agents by consultation type

Agent (ATC code)	Frequency by type of enquiry (n (%))	
	Selection	Adverse effect
Rituximab (L01XC02)	51 (71.8)	20 (28.2)
Infliximab (L04AB01)	10 (17.9)	46 (82.1)
Adalimumab (L04AB04)	20 (36.4)	35 (63.6)
Etanercept (L04AB01)	14 (31.1)	31 (68.9)
Omalizumab (R03DX05)	29 (90.6)	3 (9.4)
Natalizumab (L04AA23)	11 (44.0)	14 (56.0)
Anakinra (L04AC03)	13 (92.9)	1 (7.1)
Denosumab (M05BX04)	8 (57.1)	6 (42.9)
Ustekinumab (L04AC05)	9 (64.3)	5 (35.7)
Other	33 (56.9)*	25 (43.1)†

The percentages indicate the proportion of consultations for that specific agent that were placed under the corresponding heading.

*Abciximab, aflibercept, belimumab, bevacizumab, canakinumab, certolizumab, cetuximab, gemtuzumab, golimumab, ofatumumab, palivizumab, ranibizumab, tocilizumab and trastuzumab.

†Abatacept, abciximab, basiliximab, bevacizumab, cetuximab, daclizumab, efalizumab, ofatumumab, onartuzumab, ranibizumab, tocilizumab and trastuzumab.

Box 1 Some examples of enquiries about selection and adverse effects

Some questions about selection:

- Is anakinra indicated in a patient with familial Mediterranean fever unresponsive to colchicine?
- Is rituximab a good option in a patient with systemic sclerosis-associated lung disease?
- About suitability of treatment with omalizumab in a patient with food allergy and anaphylaxis.
- Appropriateness for using rituximab in a patient with primary Sjögren's syndrome.

Some questions about adverse effects:

- Which are the main dermatological adverse effects with anti-tumor necrosis factor (TNF) like adalimumab, etanercept or infliximab?
- Is it possible to administer vaccines in patients with multiple sclerosis that are treated with natalizumab?
- Teratogenic risk with daclizumab and mycophenolate mofetil in a woman whose husband received these drugs.
- What is the teratogenic risk if a patient is treated with rituximab?

Rituximab, infliximab and adalimumab were the BA most often enquired about (their sum amounts to 51.2% of the total number of consultations about BA). Although, this observation could simply reflect the fact that they are also the most frequently prescribed BA, they are often used off-label,¹⁹ and many enquiries are related with this kind of use. Evidence on the use of these medicines in unapproved indications is often scarce, and their use in these conditions is done with more uncertainty. Doctors and medical directors in a hospital setting need information to balance the efficacy, risk and cost of their use in unapproved conditions before deciding about their use for a specific patient. Even though more evidence from clinical trials would be desirable, these studies would be understandably difficult to carry out. In this setting, a register of off-label treated patients could provide valuable information and assist in prescribing decisions in clinical practice.²⁰

A large number of consultations were made regarding adverse effects, and a significant proportion of them were made to request information about their teratogenic potential. This is not surprising because data regarding their safety during pregnancy is scarce, and there is some controversy about the use of BA, such as anti-TNF drugs, in pregnant women.^{21 22} Thus, the use of BA during pregnancy (and notably those agents that may be used for conditions that affect female patients during their reproductive years), seems to be an area that merits further research.^{23 24} Anti-TNF drugs can cross the placenta from the latter part of the second trimester of gestation, although, they seem to be safe in the short term.²⁵ However, pregnancy outcomes of women on adalimumab, infliximab, etanercept, certolizumab pegol or golimumab were evaluated in a recently published prospective cohort study²⁶ that concluded that TNF- α inhibitors may carry a risk of adverse pregnancy

Table 3 Summary of indications for which selected agents enquired about had been used

	Approved indication	Off-label use enquired about
Rituximab	Rheumatoid arthritis (3) Wegener's granulomatosis (3) Non-Hodgkin's lymphoma	Systemic lupus erythematosus (12) Systemic sclerosis (7) Idiopathic thrombocytopenic purpura (3) Optic neuritis (3) Sjögren's syndrome (3) Cryoglobulinaemia (2) Dermatomyositis (2) Mixed connective tissue disease (2) Multiple sclerosis (2) Pemphigus (2) Relapsing polychondritis (2) Other (4)
Omalizumab	Asthma (6)*	Chronic urticaria (12) Anaphylaxis (5) Food allergy (3) Other (3)
Adalimumab	Rheumatoid arthritis (3)	Behçet's disease (4) Hidradenitis suppurativa (3) Pyoderma gangrenosum (3) Uveitis (2) Other (5)
Etanercept	Rheumatoid arthritis (3)* Ankylosing spondylitis (1)	Idiopathic thrombocytopenic purpura (2) Mixed connective tissue disease (2) Other (6)
Anakinra	Juvenile rheumatoid arthritis Rheumatoid arthritis	Familial Mediterranean fever (4) Hereditary autoinflammatory diseases (3) Other (4)
Infliximab	Rheumatoid arthritis (2)	Behçet's disease (2) Other (6)
Total	24 (17.5%)	113 (82.5%)

For indications with more than a single enquiry, the total number of cases is indicated in parenthesis.

*In one case, the agent was used before regulatory approval.

outcomes of moderate clinical relevance. Teratology information services²⁷ may be a useful tool in this scenario. Likewise, a register of patients for which a therapeutic consultation about drug exposures during pregnancy was made to our service is in process, in order to record the outcomes of these pregnancies. Besides their teratogenic effects, our results highlight other potential risks of BA. This may be especially important, because some of them are potentially serious.

As with any other uncertainty areas, studies that shed light on obscure aspects about the efficacy and toxicity of BA are needed. Data for these studies could come from programmes of spontaneous reporting of adverse reactions²⁸ or from other pharmacoepidemiological designs.²⁹

Our study's limitations include the fact that it was retrospective and that our therapeutic consultations centre is highly specialised (for which reason our results may not be extrapolated to those of other therapeutic information centres). However, as strengths, this is the first study assessing enquiries about BA to a therapeutic consultation service. Although our approach does not allow for conclusions on the pattern of BA usage to be drawn, it may have identified areas in which specific research may prove clinically useful.

The analysis of queries to therapeutic consultation services may identify the main areas of doubt regarding BA use in clinical practice. As such, it may be a useful tool to guide research aimed to assist in 'real world' prescribing decisions. Given the fact that clinical trials in many of these situations may be unfeasible, registration and monitoring of patients for which a situation of uncertainty has prompted a therapeutic consultation may prove a valuable alternative to improve, at least to some extent, the knowledge on these drugs.

What this paper adds

What is already known on this subject

- Upon market approval, information on a drug's efficacy and safety is scarce.
- Prescribers using newly marketed drugs are faced with many uncertainties.
- Drug information services may contribute to identify those that are most significant in clinical practice.

What this study adds

- The appropriate use of biologicals in off-label indications and their potential teratogenic effects are a source of concern to prescribers.
- Research in the aforementioned fields is a clinical need.

Competing interests None declared.

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